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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/601,490	09/21/2000	Desire Jose Collen	702-001463	5827

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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	13

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/601,490	Applicant(s) COLLEN, DESIRE JOSE	
	Examiner Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on th cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-60* is/are pending in the application.

4a) Of the above claim(s) *31-38,42,44,48-50 and 52-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-41,43,45-47 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 September 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *alignment* .

DETAILED ACTION

Status of the Application

Claims 31-60 are pending.

Applicant's election with traverse of Group CXXXIV, claims 39-41, 43, 45-47, and 51 drawn to a staphylokinase derivative having the code SY19 (S3C-MP5), in Paper No. 12, filed on 2/15/2002 is acknowledged.

Applicant's traverse is on the ground(s) that the claims are now amended so that they are drawn to "pegylated" staphylokinase derivatives instead of staphylokinase derivatives with reduced immunogenicity as originally filed. Applicants assert that since "pegylated" staphylokinase derivatives were not known before the priority date of the instant application, the inventions of Groups I-CXL now include a special technical feature ("pegylated") that links the groups of the invention as to form a single inventive concept.

Applicant's arguments have been fully considered but are not found persuasive. The inventions of the instant application are related by virtue of being drawn to staphylokinase derivatives with reduced immunogenicity. As Applicant asserts, the pegylation of the staphylokinase derivatives renders a staphylokinase derivative with reduced immunogenicity, therefore the amended claims are still drawn to staphylokinase derivatives with reduced immunogenicity. The special technical feature linking Groups I-CXL was known in the prior art, as indicated in the previous Office Action, therefore the technical feature linking inventions I-CXL does not constitute a special technical feature as defined by PCT Rule 13.2.

The requirement is deemed proper and therefore is made FINAL.

Claims 31-38, 42, 44, 48-50, and 52-60 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. It is noted that some of the claims in the elected group are drawn in part to non-elected inventions. Examination of such claims will be limited to the subject matter elected, which in the instant case is the staphylokinase derivative labeled SY19(S3C-MP5). Applicant is requested to amend the claims accordingly, in particular, claim 43, which encompasses other staphylokinase derivatives not elected.

Specification

1. The word "cystein" should be "cysteine". Correction is required in the specification and in the claims.

2. The disclosure is objected to for not complying with sequence rules. Applicant is required to insert sequence identifiers in front of sequences referred to in the specification (37 CFR 1.821(d)). See, for example, page 8 of the specification. Applicant is requested to make the appropriate changes throughout the specification.

3. The disclosure is objected to for not complying with the preferred layout and content for the application. In particular, the instant application lacks headings for Background of the Invention, Brief Summary of the Invention, Brief Description of the Drawings, etc. See 37 CFR 1..77(b). Correction is required.

4. The abstract of the disclosure is objected to because of its length. It exceeds the 150-word limit. Correction is required. See MPEP § 608.01(b).

Drawings

5. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Objections

6. It is noted that amino acids are being recited in the claims either with the 3-letter code or by using the full name. It is suggested that only one way of naming amino acids be used throughout the claims for consistency.

7. Claim 39 is objected to because of the following informalities: for clarity, it is suggested that the limitations recited after the word "following" be numbered (i.e. (i), (ii) or (a), (b)).

8. Claim 40 is objected to because of the recitation of "SakSTAR". Abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

9. Claim 46 is objected to because of the following informalities: for clarity, it is suggested that the claim be amended to clearly indicate the characteristics of the claimed derivative as

follows: "The staphylokinase derivatives of claim 45 wherein, (a) selected....., and (b) said derivatives are characterized by .....".

10. Claim 51 is objected to because of the following informalities: for clarity, it is suggested that the claim be amended to clearly indicate the modifications of the staphylokinase derivative claimed as follows: "The staphylokinase derivative of claim 47 labeled SY19(S3C-MP5), wherein said derivative comprises amino acid substitutions S3C, E65D, K74R, E80A, D82A, K130T, K135R, and wherein the cysteine at position 3 is chemically modified with MAL-PEG 5 KDa.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 39-41, 43, and 45-47 (claim 51 dependent thereon) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claims 39, 40, 41, and 43 are indefinite in the recitation of "amino acid sequence as depicted in figure 1" as it is unclear which amino acid sequence is being referred to absent a sequence identifier. It is suggested that if the sequence of Figure 1 is in the Sequence Listing, a numerical sequence identifier be used (SEQ ID NO: #). See 37 CFR 1.821(d). For examination purposes, the amino acid sequence of Figure 1 will be interpreted as being the amino acid sequence of SEQ ID NO: 1. Correction is required.

13. Claim 39 is indefinite in the recitation of "reducing reactivity with a panel of murine monoclonal antibodies" as it is unclear which monoclonal antibodies are being referred to. As written, one cannot determine if the recited antibodies can have any specificity or if the antibodies are specific to staphylokinase. It is suggested that if Applicant's intended antibodies are specific towards staphylokinase, the claim be amended to clearly identify the specificity of the monoclonal antibodies. For examination purposes, the language "panel of murine monoclonal antibodies" will be interpreted as "any murine monoclonal antibody". Correction is required.

14. Claim 39 is indefinite in the recitation of "at least one amino acid substituted with Cys" and "polyethylene glycol substitution" for the following reasons. First, it is unclear which amino acids are encompassed by the claim since it is not expected that any amino acid substituted with Cys will result in increased specific activity, reduced clearance, or thrombolytic potency. Second, it is unclear from the claim as written, where the polyethylene glycol substitution is being made which will result in reduced plasma clearance. It is suggested that Applicant clearly indicate which amino acids are being substituted with Cys and where the polyethylene glycol substitution takes place. For examination purposes, the terms "at least one amino acid substituted" and "polyethylene glycol substitution" will be interpreted as "any number of amino acids substituted" and "polyethylene glycol substitution anywhere", respectively. Correction is required.

15. Claim 41 is indefinite in the recitation of "without reducing the specific activity by more than 50 percent" as it is unclear without a basis for comparison. The term "specific activity by more than 50% percent" is a relative term and neither the claim nor the specification provide a

standard for ascertaining the requisite degree. Therefore one of skill in the art cannot reasonably apprised of the scope of the invention. It is suggested that if Applicant's basis for comparison is the specific activity of the wild type staphylokinase, the claim be amended as follows: "The staphylokinase derivatives of claim 39 .....wherein the specific activity of said derivatives is at least 50% that of the corresponding wild-type staphylokinase". For examination purposes, the claim will be interpreted as being directed to derivatives wherein the specific activity of said derivatives is at least 50% that of the corresponding wild-type staphylokinase. Correction is required.

16. Claim 43 is indefinite in the recitation of "in which the indicated amino acids have been replaced by other amino acids" as it is unclear what the subject matter claimed is. As written, one cannot determine if the claim is drawn to variants (due to amino acid substitutions) of the derivatives listed in Tables 1, 3-8, 13, 19 and 20 or if the claim is specifically drawn to the derivatives listed in Tables 1, 3-8, 13, 19 and 20. It is suggested that if Applicant's intended derivatives are the ones listed in Tables 1, 3-8, 13, 19 and 20, the term "in which the indicated amino acids have been replaced by other amino acids" be removed. As indicated above, this claim will be interpreted as being directed to the elected derivative, SY19(S3C-MP5) for examination purposes. Correction is required.

17. Claims 45 and 46 are indefinite in the recitation of "chemically modified with polyethylene glycol with molecular weights up to 20 KDa" as it is unclear whether the molecular weights recited in the claims refer to polyethylene glycol or the staphylokinase derivatives. It is suggested that if the molecular weights recited in the claim refer to polyethylene glycol, the language of the instant claim be replaced with more clear and unambiguous language, such as

"chemically modified with polyethylene glycol, wherein the polyethylene glycol can have a molecular weight of up to 20 KDa". Correction is required.

18. Claim 46 is indefinite in the recitation of "amino acids in the NH_2-terminal region of 10 amino acids are substituted with Cys" for the following reasons. First, a sequence identifier is needed to identify the sequence which the "10 amino acids" recited in the claim belong to. Second, it is unclear which 10 amino acids within the NH_2-terminal region are being referred to. It is suggested that the claim be amended to clearly indicate the location of the "10 amino acids" within the NH_2-terminal region, by using a sequence identifier and the corresponding positions (i.e. SEQ ID NO: # positions #-#). Correction is required.

19. Claim 47 is indefinite in the recitation of "wherein the serine in position 2 or 3 is substituted with a cystein" as it is unclear which position is being referred without indicating the specific sequence to which positions 2 or 3 belong to. It is suggested that Applicants amend the claim to include a numerical sequence identifier (SEQ ID NO: #) if the sequence has been disclosed in the Sequence Listing to clearly identify the sequence which positions 2 or 3 belong to. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 39, 40, and 41 (claims 45 and 46 dependent thereon) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Adequate description of the species encompassed by the claim would have relevant identifying characteristics which include (1) structure, (2) physical and/or chemical characteristics, (3) functional characteristics when coupled with a known or disclosed correlation between function and structure, (4) a combination of identifying characteristics sufficient to show that Applicant was in possession of the claimed genus.

Claims 39-41 are directed to genera of staphylokinase derivatives wherein such derivatives are the result of any number of amino acid substitutions and further including (a) amino acid substitutions with Cys, (b) polyethylene glycol substitutions anywhere within the polypeptide, or (c) staphylokinase derivatives having at least 50% of the specific activity of the corresponding wild-type staphylokinase. Applicant discloses a number of active staphylokinase derivatives wherein specific amino acid residues have been substituted. While the specification discloses some structural elements sensitive to modifications which would lead to inactivation of the staphylokinase (page 2, lines 25-29), no disclosure of which structural elements can be modified and still maintain 50% or more of the specific activity of the corresponding wild-type staphylokinase has been provided. In addition, the state of the art teaches that not all variants of a polypeptide will retain function. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a

hydrolase to a desaturase. Many functionally unrelated polypeptides are encompassed within the scope of these claims. The specification only discloses some species which is insufficient to put one of ordinary skill in the art in possession of the attributes and features of all species within the claimed genera. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

21. Claims 39, 40, and 41 (claims 45 and 46 dependent thereon) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the elected staphylokinase derivative SY19 (S3C-MP5), does not reasonably provide enablement for any staphylokinase derivative which results from any number of amino acid substitutions including (a) substitutions with Cys, (b) polyethylene glycol substitutions anywhere within the polypeptide or (c) any staphylokinase derivative having at least 50% of the specific activity of the corresponding wild-type staphylokinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claims 39-41 encompass any staphylokinase derivative (variant) wherein such derivatives are the result of any number of amino acid substitutions and further including (a)

amino acid substitutions with Cys, (b) polyethylene glycol substitutions anywhere within the polypeptide, or (c) staphylokinase derivatives having at least 50% of the specific activity of the corresponding wild-type staphylokinase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of derivatives broadly encompassed by the claim. While the specification discloses the structure and function of the polypeptide of Figure 1 (assumed to be SEQ ID NO: 1) and two structural elements known to affect the activity of the staphylokinase (page 2, lines 25-29), no disclosure of the critical structural elements required in any derivative of SEQ ID NO: 1 to retain at least 50% of the specific activity of the corresponding wild-type staphylokinase has been presented. In the absence of this information, one of skill in the art would not know which variants of the polypeptide of SEQ ID NO: 1 are likely to have staphylokinase activity. In addition, since some of the claims encompass derivatives which are no longer functional as staphylokinases, it is unclear how those derivatives can have Applicant's intended used. Since not all derivatives (variants) are expected to have the desired function, one of skill in the art would have to test an infinite number of variants of the polypeptide of SEQ ID NO: 1 to determine if they have the desired activity. Therefore, due to the lack of relevant examples, the amount of information provided, and the lack of knowledge about the critical structural elements required to maintain the desired function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those molecules, as encompassed by the claim, with the desired activity. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

22. Claims 39-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Behnke et al. (US Patent No. 5,801,037, filed on June 30, 1994, published on September 1, 1998). Behnke et al. teaches a staphylokinase variant of SEQ ID NO: 1 wherein a methionine residue at position 26 has been substituted with a cysteine residue.

Claims 39-41 are directed in part to staphylokinase derivatives of SEQ ID NO: 1 wherein one or more amino acids have been replaced by a cysteine residue, therefore the staphylokinase of Behnke et al. anticipates the claims as written.

Double Patenting

23. It is noted that the subject matter of applications Serial No. 09/728,670 and 09/020,018 appears to be overlapping with the subject matter of the instant application. Since applications Serial No. 09/728,670 and 09/020,018 are not available to the Examiner at this time, no

determination has been made as to whether or not a double patenting rejection should be applied to the claims of the instant application. If, upon availability of the above applications to the Examiner, it is determined that there are conflicting claims between applications Serial No. 09/728,670 and 09/020,018 and the instant application, double patenting will not be considered as new ground(s) of rejection.

Conclusion

24. No claim is in condition for allowance.

25. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

26. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 29, 2002

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